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(21) Application number: **93108599.7**(22) Date of filing: **27.05.1993****(54) Hair-growing composition containing prostaglandin I₂ derivatives**Prostaglandin-I₂-Derivate enthaltende HaarwuchsmittelComposition capillaire contenant des dérivés de prostaglandine I₂

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Description**BACKGROUND OF THE INVENTION**5 **I. Field of the Invention**

This invention relates to a composition for stimulating growth of hair.

10 **II. Description of the Related Art**

15 Prostaglandin I₂ (PGI₂, prostacyclin) is a substance known to have strong platelet-aggregation inhibition activity and vasodilating activity. However, since PGI₂ has an unstable exoenol structure, it is extremely unstable even in neutral aqueous solution and is easily converted to 6-oxo-PGF1 α which has substantially no activities. The instability of PGI₂ is a great problem in using this compound as a pharmaceutical. Furthermore, PGI₂ is unstable in the body and its duration of pharmacological activity is short. To eliminate these drawbacks of PGI₂, PGI₂ derivatives in which the characteristic exoenol ether moiety of PGI₂ is converted to inter-m-phenylene have been proposed in, for example, Japanese Laid-open Patent Application (Kokai) Nos. 57-32277, 57-144276 and 58-124778. Derwent Publications AN-86-295722 and patent JP-A-61 218 510 disclose hair cosmetic compositions comprising PGE₁ and/or PGI₂ as effective ingredients against alopecia. However, there is no disclosure or suggestion in these and other published references that these PGI₂ derivatives have activities to stimulate hair growth and so the usefulness for the treatment of alopecia.

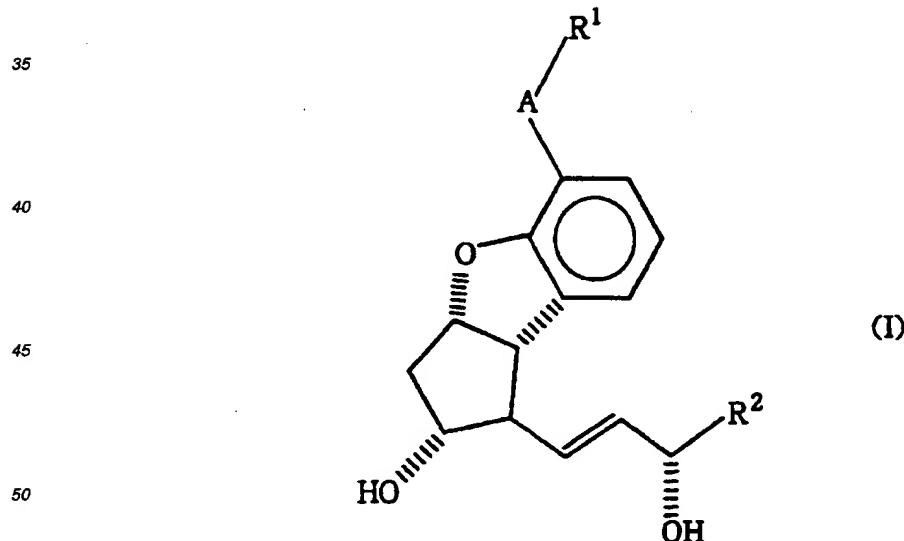
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SUMMARY OF THE INVENTION

Accordingly, an object of the present invention is to provide a composition for stimulating or promoting hair growth
25 of an animal including human. Another object of the present invention is to provide a new use of the known PGI₂ derivatives.

The present inventors intensively studied to find that the PGI₂ derivatives have activities to stimulate or promote hair growth of animals including human, thereby completing the present invention.

That is, the present invention provides a hair-growing composition comprising a 5,6,7-trinor-4,8-inter-m-phenylene
30 prostaglandin I₂ derivative of the formula (I) below or a pharmaceutically acceptable salt thereof in a pharmaceutically acceptable vehicle in an amount effective for stimulating growth of hair:



55 (wherein

R¹ represents hydrogen, carboxylic group or a functional derivative thereof, -CH₂OH or a pharmaceutically acceptable cation;

A represents

- 5
 (i) $-(CH_2)_n-$,
 (ii) $-(CH_2)_m-CH=CH-(CH_2)_p-$,
 (iii) $-(CH_2)_m-C=C-(CH_2)_p-$ or
 (iv) $-CH_2-O-CH_2-$

(wherein n represents an integer of 0 - 3, m and p, the same or different, represent 0 or 1);
 R² represents

- 10
 (i) C₅ - C₁₀ straight or branched alkyl group,
 (ii) -C_tH_{2t}-OR³ (wherein t represents an integer of 1 - 5, R³ represents C₁ - C₅ straight or branched alkyl group or phenyl group),
 (iii) -C_tH_{2t}-CH=C(R⁴)(R⁵) (wherein t represents the same meaning as mentioned above, R⁴ and R⁵, the same or different, represent hydrogen, methyl, ethyl, propyl or butyl group), or
 15 (iv) -C_tH_{2t}-C=C-R⁶ (wherein t represents the same meaning as mentioned above, R⁶ represents hydrogen, methyl or ethyl group, and -C_tH_{2t} in (ii), (iii) and (iv) represent straight or branched alkylene group);

wherein said compound of the formula (I) may be d-, l- or dl-form.

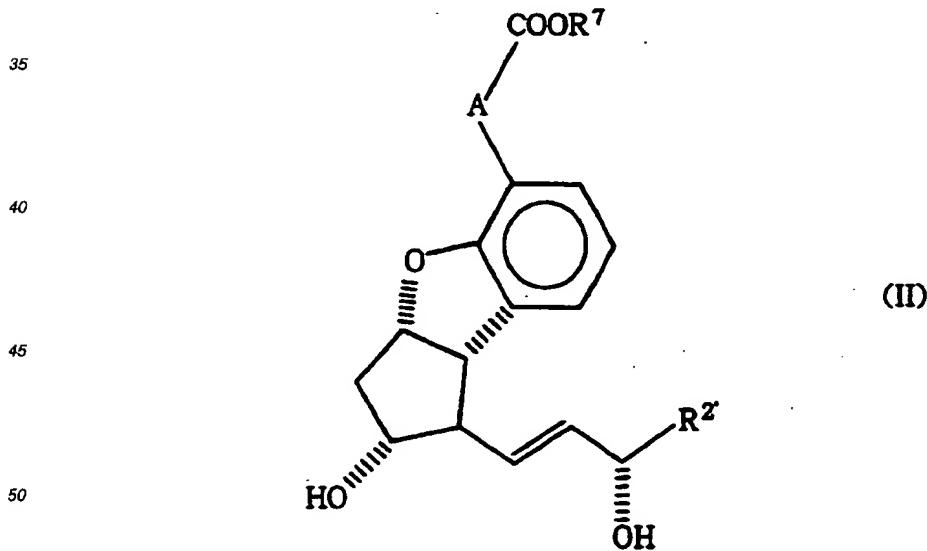
The present invention also provides a use of a 5,6,7-trinor-4,8-inter-m-phenylene prostaglandin I₂ derivative of the above-described formula (I) or a pharmaceutically acceptable salt thereof as a hair-growing agent.

20 The hair-growing composition exhibits high activity to stimulate or promote hair growth in animals including human when orally or parenterally administered.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

25 As described above, the effective ingredient having hair-growing activity in the composition according to the present invention is represented by the above-described formula (I). The functional derivative of carboxylic group for R¹ means the derivative of identical function, such as carboxylic esters. The pharmaceutically acceptable cation for R¹ may be an alkaline metal or an alkaline earth metal such as sodium, potassium or calcium. The compound represented by the formula (I) may be optically active d-form (d-optical isomer) or l-form (l-optical isomer) or may be racemate body (dl-form).

30 Among the PGI₂ derivatives represented by the formula (I), preferred are those represented by the formula (II):



55 (wherein

R⁷ represents methyl or ethyl, a pharmaceutically acceptable alkaline metal or alkaline earth metal, or an amine or basic amino acid;

A represents

- 5
 (i) $-(\text{CH}_2)_n-$.
 (ii) $-(\text{CH}_2)_m-\text{CH}=\text{CH}-(\text{CH}_2)_p-$.
 (iii) $-(\text{CH}_2)_m-\text{C}=\text{C}-(\text{CH}_2)_p-$ or
 (iv) $-\text{CH}_2-\text{O}-\text{CH}_2-$

(wherein n' represents an integer of 1 - 3, m and p represent the same meanings as in formula (I));
 R² represents

- 10 (i) C₅ - C₇ straight or branched alkyl group,
 (ii) -C_tH_{2t}-OR³ (wherein t represents an integer of 1 - 3, R³ represents C₂ - C₄ straight or branched alkyl group or phenyl group,
 (iii) -C_tH_{2t}-CH=C(R⁴)(R⁵) (wherein t represents the same meaning as mentioned above, R⁴ and R⁵ represent the same meanings as in formula (I)), or
 (iv) -C_tH_{2t}-C=C-R⁶
 15 (wherein t represents the same meaning as mentioned above, R⁶ represents the same meaning as in formula (I), and -C_tH_{2t} in (ii), (iii) and (iv) represent straight or branched alkylene group);

wherein said compound of the formula (II) may be d-, l- or dl-form.

In the formula (II), the pharmaceutically acceptable alkaline metal or alkaline earth metal for R⁷ may preferably be sodium, potassium or calcium. The amine and the basic amino acid for R⁷ may preferably be one selected from the group consisting of monomethylamine, dimethylamine, trimethylamine, methylpyridine, monoethanolamine, diethanolamine, triethanolamine and lysine.

As mentioned above, the PGl₂ derivatives represented by the formula (I) *per se* are known and the production processes thereof are described in, for example, U.S. Patent No. 4,474,802.

The compounds represented by the formula (I) exhibit hair-growing activities when administered orally or parenterally.

The compounds represented by the formula (I) may usually be administered in a dose of 0.01 - 100 mg/body and 1 - 3 times a day (i.e., 0.01 - 300 mg/body/day).

Although the compounds represented by the formula (I) alone can be administered, they can also be administered together with a pharmaceutically acceptable vehicle.

For oral administration, the active compound may be formulated with a pharmaceutically acceptable vehicle to form a solid composition. Preferred examples of the pharmaceutically acceptable vehicle used for this purpose include starches, lactose, sucrose, glucose, mannitol, calcium carbonate, calcium sulfate and the like. The composition may also contain a binding agent such as starch, dextrin, gum arabicae, tragacanth, methyl cellulose, gelatin, polyvinylpyrrolidone, polyvinyl alcohol or the like; a disintegrator such as starch, polyvinylpyrrolidone, crystalline cellulose or the like; a lubricant such as magnesium stearate, talc or the like; a coloring agent; and a perfume.

The formulation for oral administration may be in the form of tablets, sugar-coated tablets, powder, granules, troches, capsules, balls and syrups.

For parenteral administration, the composition may be formulated into an aqueous sterilized solution for injection (subcutaneous, intravenous, intramuscular, intraperitoneal or the like). The solution may contain other solutes such as sodium chloride or glucose in an amount sufficient to make the solution isotonic.

The concentration of the active ingredient in the composition for oral or parenteral administration is not restricted and may usually be 0.1 ng/ml to 500 µg/ml.

Since the compound of the formula (I) has a stable chemical structure, there is no difficulty in formulating the compound. Thus, in addition to the above-described formulations for oral administration and for injection, the compound may easily be formulated in the form of an absorption-promoting agent, a topical formulation such as ointment, and in the form of a suppository.

The present invention will now be described by way of examples thereof. It should be noted that the examples are presented for the illustration purpose only and should not be interpreted in any restrictive way.

50
Example

The compound having a structure shown in Table 1 (beraprost) was tested for its hair-growing activity using male New Zealand white rabbits weighing 2 - 3 kg. In Table 1, the groups R¹, R² and A in formula (I) are shown.

Table 1

R ¹ :	-COONa
R ² :	-CH(CH ₃)-CH ₂ -C=C-CH ₃
A:	-(CH ₂) ₃ -

5

10

Each group consisted of 3 - 4 rabbits. The hair on the back of each rabbit was shaved. The test compound was administered to each rabbit every day for two weeks and the length of the hair newly grown on the shaved back was measured.

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More particularly, for subcutaneous administration, the test compound was dissolved in physiological saline to a concentration of 400 µg/ml and 0.25 ml/kg body weight of the solution was administered to each rabbit at one time every day. For oral administration, the test compound was dissolved in distilled water to a concentration of 400 µg/ml and 0.25 ml/kg body weight of the solution was administered to each rabbit at one time every day. After the oral administration, the solution remaining in the oral administration tube was forced into the body with 3 ml of distilled water. As a control, 0.25 ml/kg body weight of physiological saline was subcutaneously administered. Five or more hairs were collected from five regions in the shaved back and the lengths of the hairs were measured. The results are shown in Table 2.

20

As shown in Table 2, the test compound significantly increased the length of the newly grown hair when compared with the control group.

25

Table 2

Test Compound	Administration Route	Dose	Length of Hair (mm)
Control	Subcutaneous	0.25ml/kg	2.38 ± 0.07
Beraprost	Subcutaneous	0.1 mg/kg	4.54 ± 0.31
	Oral	0.1 mg/kg	3.92 ± 0.24

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Claims

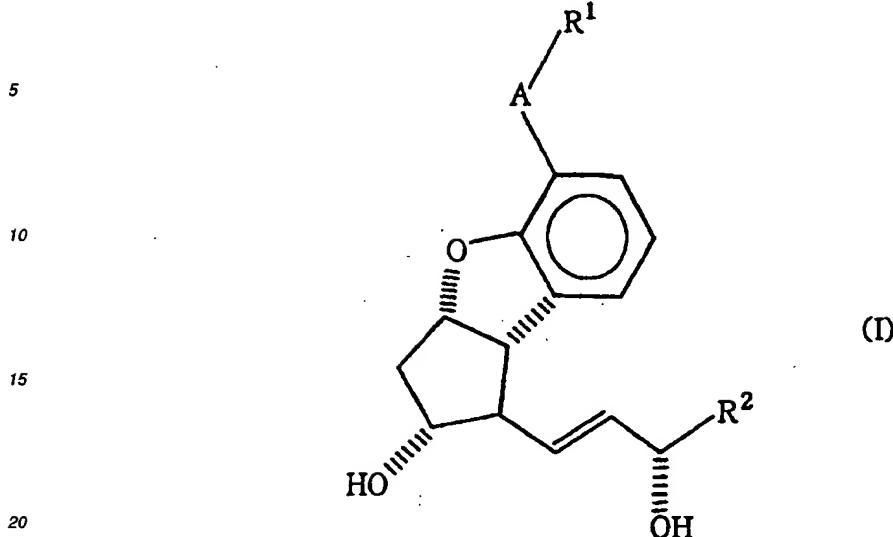
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1. Use as a hair growth promoting agent of a composition comprising a 5,6,7-trinor-4,8-inter-m-phenylene prostaglandin I₂ derivative of the formula (I) below or a pharmaceutically acceptable salt thereof in a pharmaceutically acceptable carrier in an amount effective for stimulating growth of hair:

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50

55



(wherein

25 R¹ represents hydrogen, carboxylic group or a functional derivative thereof, -CH₂OH or a pharmaceutically acceptable cation;
 A represents

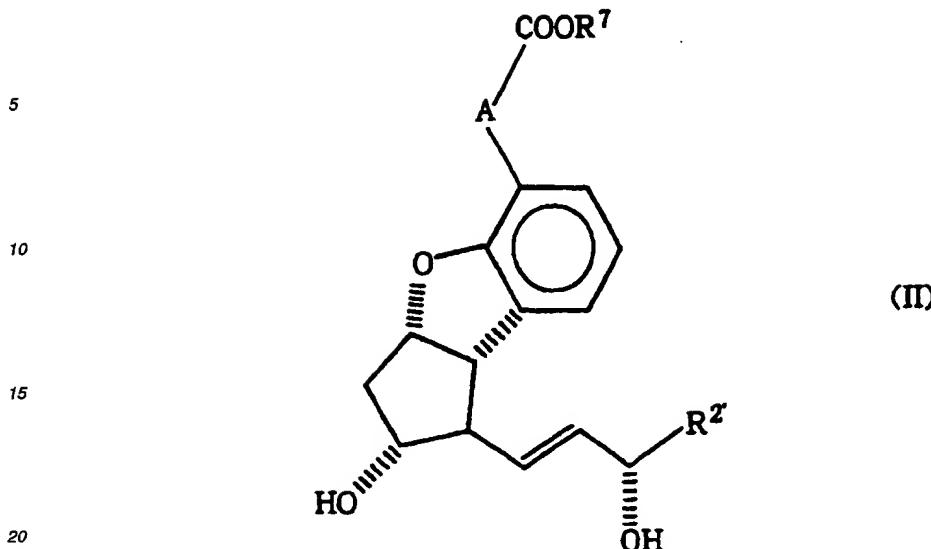
- 30 (i) -(CH₂)_n;
 (ii) -(CH₂)_m-CH=CH-(CH₂)_p;
 (iii) -(CH₂)_m-C=C-(CH₂)_p or
 (iv) -CH₂-O-CH₂-

35 (wherein n represents an integer of 0 - 3, m and p, the same or different, represent 0 or 1);
 R² represents

- 40 (i) C₅ - C₁₀ straight or branched alkyl group,
 (ii) -C_tH_{2t}-OR³ (wherein t represents an integer of 1 - 5, R³ represents C₁ - C₅ straight or branched alkyl group or phenyl group),
 (iii) -C_tH_{2t}-CH=C(R⁴)(R⁵)
 (wherein t represents the same meaning as mentioned above, R⁴ and R⁵, the same or different, represent hydrogen, methyl, ethyl, propyl or butyl group), or
 (iv) -C_tH_{2t}-C=C-R⁶
 (wherein t represents the same meaning as mentioned above, R⁶ represents hydrogen, methyl or ethyl group, and -C_tH_{2t} in (ii), (iii) and (iv) represent straight or branched alkylene group);

45 wherein said compound of the formula (I) may be d-, l- or dl-form.

- 50 2. Use according to claim 1, wherein said 5,6,7-trinor-4,8-inter-m-phenylene prostaglandin I₂ derivative is represented by the formula (II):



(wherein

25 R^7 represents methyl or ethyl, a pharmaceutically acceptable alkaline metal or alkaline earth metal, or an amine or basic amino acid;

A represents

- 30 (i) $-(CH_2)_n-$,
(ii) $-(CH_2)_m-CH=CH-(CH_2)_p-$,
(iii) $-(CH_2)_m-C=C-(CH_2)_p-$ or
(iv) $-CH_2-O-CH_2-$

35 (wherein n' represents an integer of 1 - 3, m and p represent the same meanings as in formula (I));
 R^2' represents

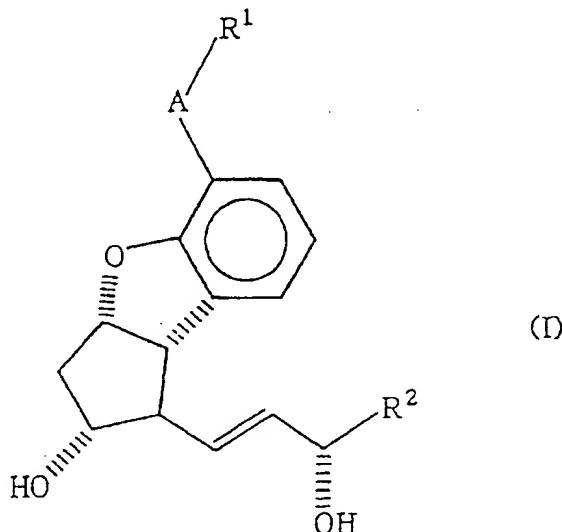
- 40 (i) $C_5 - C_7$ straight or branched alkyl group,
(ii) $-C_tH_{2t}-OR^3$ (wherein t' represents an integer of 1 - 3, R^3 represents $C_2 - C_4$ straight or branched alkyl group or phenyl group,
(iii) $-C_tH_{2t}-CH=C(R^4)(R^5)$
(wherein t' represents the same meaning as mentioned above, R^4 and R^5 represent the same meanings as in formula (I)), or
(iv) $-C_tH_{2t}-C=C-R^6$
(wherein t' represents the same meaning as mentioned above, R^6 represents the same meaning as in formula (I), and $-C_tH_{2t}$ in (ii), (iii) and (iv) represent straight or branched alkylene group);

wherein said compound of the formula (II) may be d-, l- or dl-form.

- 50 3. Use according to claim 2, wherein said alkaline metal and alkaline earth metal for R^7 is selected from the group consisting of sodium, potassium and calcium, said amine and said basic amino acid for R^7 are selected from the group consisting of monomethylamine, dimethylamine, trimethylamine, methylpyridine, monoethanolamine, diethanolamine, triethanolamine and lysine.
- 55 4. Use according to claim 3, wherein said 5,6,7-trinor-4,8-inter-m-phenylene prostaglandin I₂ derivative is beraprost or a pharmaceutically acceptable salt thereof.

Patentansprüche

1. Verwendung einer Zusammensetzung, die ein 5,6,7-Trinor-4,8-inter-m-phenylen Prostaglandin-I₂ Derivat der unten gezeigten Formel (I) oder ein pharmazeutisch annehmbares Salz davon in einem pharmazeutisch annehmbaren Träger in einer für die Anregung des Haarwuchses wirksamen Menge umfaßt, als haarwuchsförderndes Mittel:



worin R¹ Wasserstoff, eine Carboxylgruppe oder ein funktionalisiertes Derivat davon, -CH₂OH oder ein pharmazeutisch annehmbares Kation bedeutet;

A bedeutet

- (1) -(CH₂)_n-,
- (2) -(CH₂)_m-CH=CH-(CH₂)_p-,
- (3) -(CH₂)_m-C=C-(CH₂)_p- oder
- (4) -CH₂-O-CH₂-

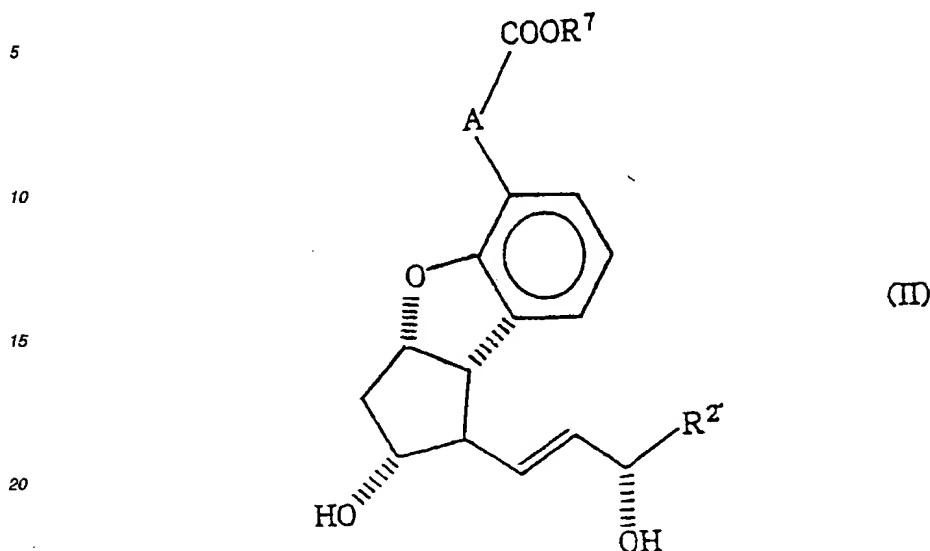
(worin n eine ganze Zahl von 0 bis 3 ist, m und p, die gleich oder unterschiedlich sind, für 0 oder 1 stehen);

R² bedeutet

- (1) eine C₅-C₁₀ kettenförmige oder verzweigte Alkylgruppe,
- (2) -C_tH_{2t}-OR³ (worin t eine ganze Zahl von 1 bis 5 ist, R³ eine C₁-C₅ kettenförmig oder verzweigte Alkylgruppe oder Phenylgruppe darstellt),
- (3) -C_tH_{2t}-CH=C(R⁴)(R⁵)
(worin t die oben genannte Bedeutung hat, R⁴ und R⁵, die gleich oder unterschiedlich sind, Wasserstoff-, Methyl-, Ethyl-, Propyl- oder Butylgruppen bedeuten) oder
- (4) -C_tH_{2t}-C=C-R⁶
(worin t die oben genannte Bedeutung hat, R⁶ Wasserstoff-, Methyl- oder Ethylgruppe bedeutet und -C_tH_{2t} in (2), (3) und (4) eine kettenförmige oder verzweigte Alkylengruppe bedeutet);

wobei die besagte Verbindung der Formel (I) in der D-, L- oder DL-Form vorliegen kann.

2. Verwendung nach Anspruch 1, dadurch gekennzeichnet, daß das besagte 5,6,7-Trinor-4,8-inter-m-phenylen Prostaglandin-I₂ Derivat durch die Formel (II) beschrieben wird:



25 (worin R⁷ Methyl oder Ethyl, ein pharmazeutisch annehmbares Alkalimetall oder Erdalkalimetall oder ein Amin oder eine basische Aminosäure bedeutet;

A bedeutet

- 30 (1) -(CH₂)_n-,
 (2) -(CH₂)_m-CH=CH-(CH₂)_p-,
 (3) -(CH₂)_m-C=C-(CH₂)_p- oder
 35 (4) -CH₂-O-CH₂-

40 (worin n' eine ganze Zahl von 1 bis 3 ist, m und p die gleiche Bedeutung wie in Formel (I) besitzen);
 R²' bedeutet:

- 45 (1) eine C₅-C₇ kettenförmige oder verzweigte Alkylgruppe,
 (2) -C_tH_{2t}-OR³ (worin t' eine ganze Zahl von 1 bis 3 ist, R³ eine C₂-C₄ kettenförmige oder verzweigte Alkylgruppe oder Phenylgruppe bedeutet),
 (3) -C_tH_{2t}-CH=C(R⁴)(R⁵) (worin t' die oben genannte Bedeutung besitzt, R⁴ und R⁵ die gleiche Bedeutung wie in Formel (I) haben), oder
 50 (4) -C_tH_{2t}-C=C-R⁶ (worin t' die oben genannte Bedeutung besitzt, R⁶ die gleiche Bedeutung wie in Formel (I) hat und -C_tH_{2t} in (2), (3) und (4) eine kettenförmige oder verzweigte Alkylengruppe bedeutet);

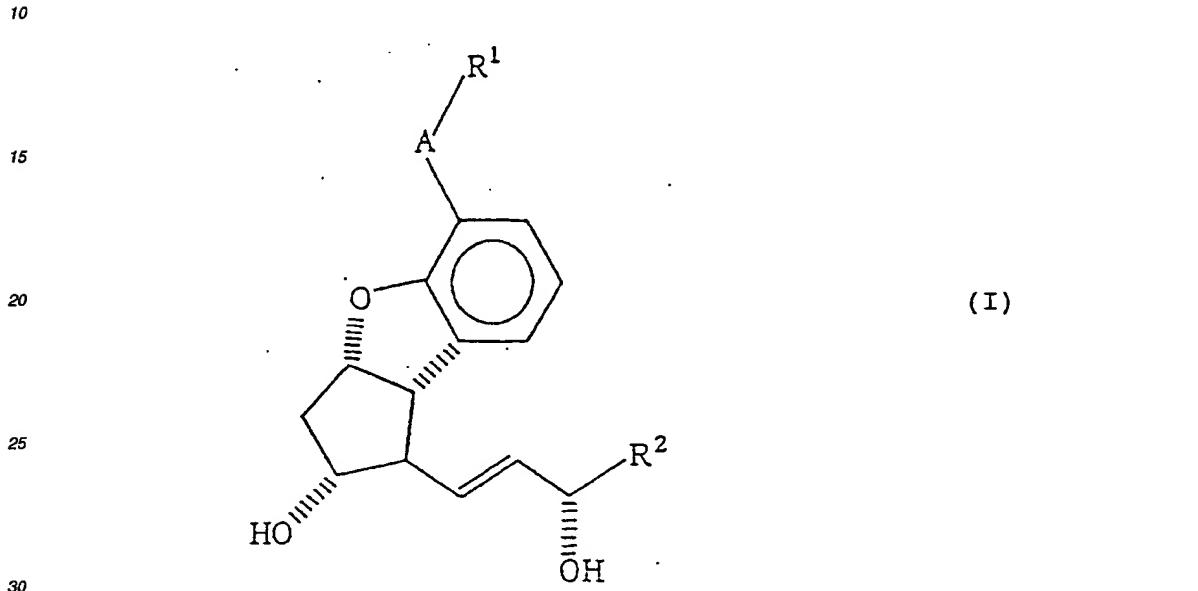
wobei die besagte Verbindung der Formel (II) in der D-, L- oder DL-Form vorliegen kann.

- 55 3. Verwendung nach Anspruch 2, dadurch gekennzeichnet, daß das besagte Alkalimetall oder Erdalkalimetall für R⁷ ein Vertreter der folgenden Gruppe, bestehend aus Natrium, Kalium und Calcium, ist, das besagte Amin und die besagte basische Aminosäure für R⁷ Vertreter der folgenden Gruppe, bestehend aus Monomethylamin, Dimethylamin, Trimethylamin, Methylpiperidin, Monoethanolamin, Diethanolamin, Triethanolamin und Lysin, sind.

4. Verwendung nach Anspruch 3, dadurch gekennzeichnet, daß das besagte 5,6,7-Trinor-4,8-inter-m-phenylen Prostaglandin-I₂ Derivat Beraprost oder ein pharmazeutisch annehmbares Salz davon ist.

Revendications

- 5 1. Utilisation comme agent favorisant la poussée des poils d'une composition comprenant un dérivé de la 5,6,7-trinor-4,8-inter-m-phénylène prostaglandine I₂ ayant la formule (I) ci-dessous ou un sel pharmaceutiquement acceptable de celui-ci dans un support pharmaceutiquement acceptable en une quantité efficace pour stimuler la poussée des poils:



(dans laquelle

35 R¹ représente un hydrogène, un groupe carboxylique ou un dérivé fonctionnel de celui-ci, -CH₂OH ou un cation pharmaceutiquement acceptable;
A représente

- 40 (i) -(CH₂)_n-,
(ii) -(CH₂)_m-CH=CH-(CH₂)_p-,
(iii) -(CH₂)_m-C=C-(CH₂)_p ou
(iv) -CH₂-O-CH₂-

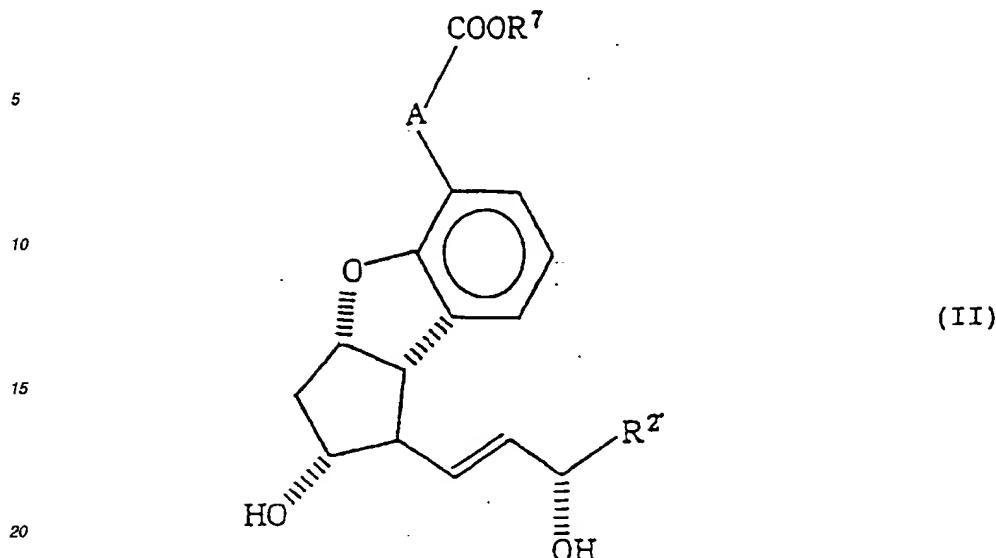
(où n représente un nombre entier de 0 - 3, m et p, identiques ou différents, représentent 0 ou 1);

45 R² représente

- (i) un groupe alkyle en C₅-C₁₀ à chaîne linéaire ou ramifiée,
(ii) -C_tH_{2t}-OR³ (où t représente un nombre entier de 1 - 5, R³ représente un groupe alkyle en C₁-C₅ à chaîne linéaire ou ramifiée ou un groupe phényle),
(iii) -C_tH_{2t}-CH=C(R⁴)(R⁵) (où t a la même signification que ci-dessus, R⁴ et R⁵, identiques ou différents, représentent un hydrogène, un groupe méthyle, éthyle, propyle ou butyle), ou
(iv) -C_tH_{2t}-C=C-R⁶
(où t a la même signification que ci-dessus, R⁶ représente un hydrogène, un groupe méthyle ou éthyle, et -C_tH_{2t} dans (ii), (iii), et (iv) représentent un groupe alkylène à chaîne linéaire ou ramifiée);

55 où ledit composé de formule (I) peut être sous la forme d, l ou dl.

2. Utilisation selon la revendication 1, dans laquelle ledit dérivé de la 5,6,7-trinor-4,8-inter-m-phénylène prostaglandine I₂ est représenté par la formule (II):



(dans laquelle

²⁵ R⁷ représente un méthyle ou un éthyle, un métal alcalin ou un métal alcalino-terreux pharmaceutiquement acceptable, ou une amine ou un acide aminé basique;
A représente

- (i) $-(CH_2)_n-$,
 - (ii) $-(CH_2)_m-CH=CH-(CH_2)_p-$,
 - (iii) $-(CH_2)_m-C=C-(CH_2)_p$ - ou
 - (iv) $-CH_2-O-CH_2-$

35 (où n' représente un nombre entier de 1 - 3, m et p ont les mêmes significations que dans la formule (I));
 R^2 représente

- (i) un groupe alkyle en C₅-C₇ à chaîne linéaire ou ramifiée,
 - (ii) -C_tH_{2t}-OR³ (où t' représente un nombre entier de 1 - 3, R³ représente un groupe alkyle en C₂-C₄ à chaîne linéaire ou ramifiée ou un groupe phényle),
 - (iii) -C_tH_{2t}-CH=C(R⁴)(R⁵) (où t' a la même signification que ci-dessus, R⁴ et R⁵ ont les mêmes significations que dans la formule (I)), ou
 - (iv) -C_tH_{2t}-C=C-R⁶ (où t' a la même signification que ci-dessus, R⁶ a la même signification que dans la formule (I), et -C_tH_{2t} dans (ii), (iii) et (iv) représentent un groupe alkylène à chaîne linéaire ou ramifiée);

45 où ledit composé de formule (II) peut être sous la forme d. I ou d.

3. Utilisation selon la revendication 2, dans laquelle ledit métal alcalin ou ledit métal alcalino-terreux pour R⁷ est choisi dans le groupe constitué par le sodium, le potassium et le calcium, ladite amine et ledit acide aminé basique pour R⁷ sont choisis dans le groupe constitué par la monométhylamine, la diméthylamine, la triméthylamine, la méthyl-pypéridine, la monoéthanolamine, la diéthanolamine, la triéthanolamine et la lysine.

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4. Utilisation selon la revendication 3, dans laquelle ledit dérivé de la 5,6,7-trinor-4,8-inter-m-phénylène prostaglandine I₂ est le beraprost ou un sel pharmaceutiquement acceptable de celui-ci